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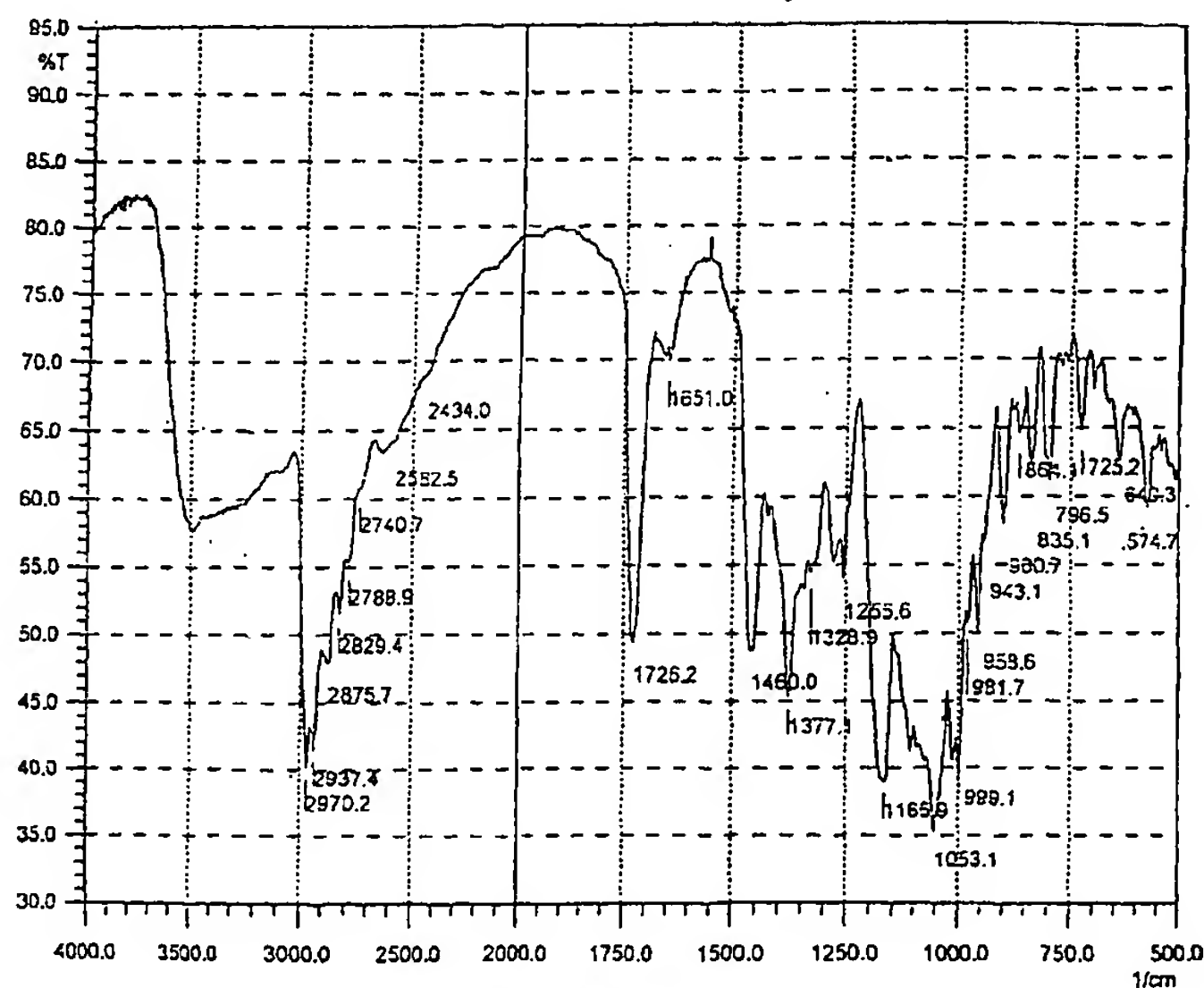
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(54) Title: PROCESS FOR PREPARATION OF ANHYDROUS AZITHROMYCIN



Infrared spectrum of anhydrous azithromycin.

(57) Abstract: The present invention provides a stable form of azithromycin derivatives that act as antibiotics. These compounds are in anhydrous form and have increased stability over the hydrated forms.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PROCESS FOR PREPARATION OF ANHYDROUS AZITHROMYCIN

Priority of Invention

5 This application claims priority from United States Provisional
Application Number 60/227,341, filed 23 August 2000, which is incorporated
herein by reference.

Background of the Invention

10 Azithromycin is a well-known semi-synthetic macrolide antibiotic. It is
prepared through the ring expansion to incorporate a nitrogen atom in the
macrolide ring of erythromycin A, followed by reductive methylation. This
provides an antibiotic having more stability and greater effectiveness than
erythromycin-A.

15 The ring expansion and subsequent conversion of erythromycin-A to
provide azithromycin is described in U.S. Patent No. 4,474,768, (*e.g.*, Example
3). Generally, the synthesis requires several steps. The product obtained is one
of the hydrated versions, either monohydrate or dihydrate.

20 Azithromycin monohydrate is hygroscopic and thus, difficult to maintain
in the monohydrated form. U.S. Patent 4,963,531 and EP application 298 650
teach a process for preparing azithromycin dihydrate. The process requires
preparing a solution of azithromycin monohydrate in tetrahydrofuran and water.
The azithromycin dihydrate is obtained by crystallization upon addition of
hexane.

25 In U.S. Patent 4,963,531 it is disclosed that on storage at low humidity
the azithromycin dihydrate loses water. In addition, samples of azithromycin
mono- and di-hydrate stored at higher humidity rapidly absorbed water. Thus,
the water percentage (percent hydration) in the crystals can vary depending on
the relative humidity during storage. This variability of the percent hydration

can make it difficult to accurately determine the proper amount of active ingredient needed to prepare various dosage forms.

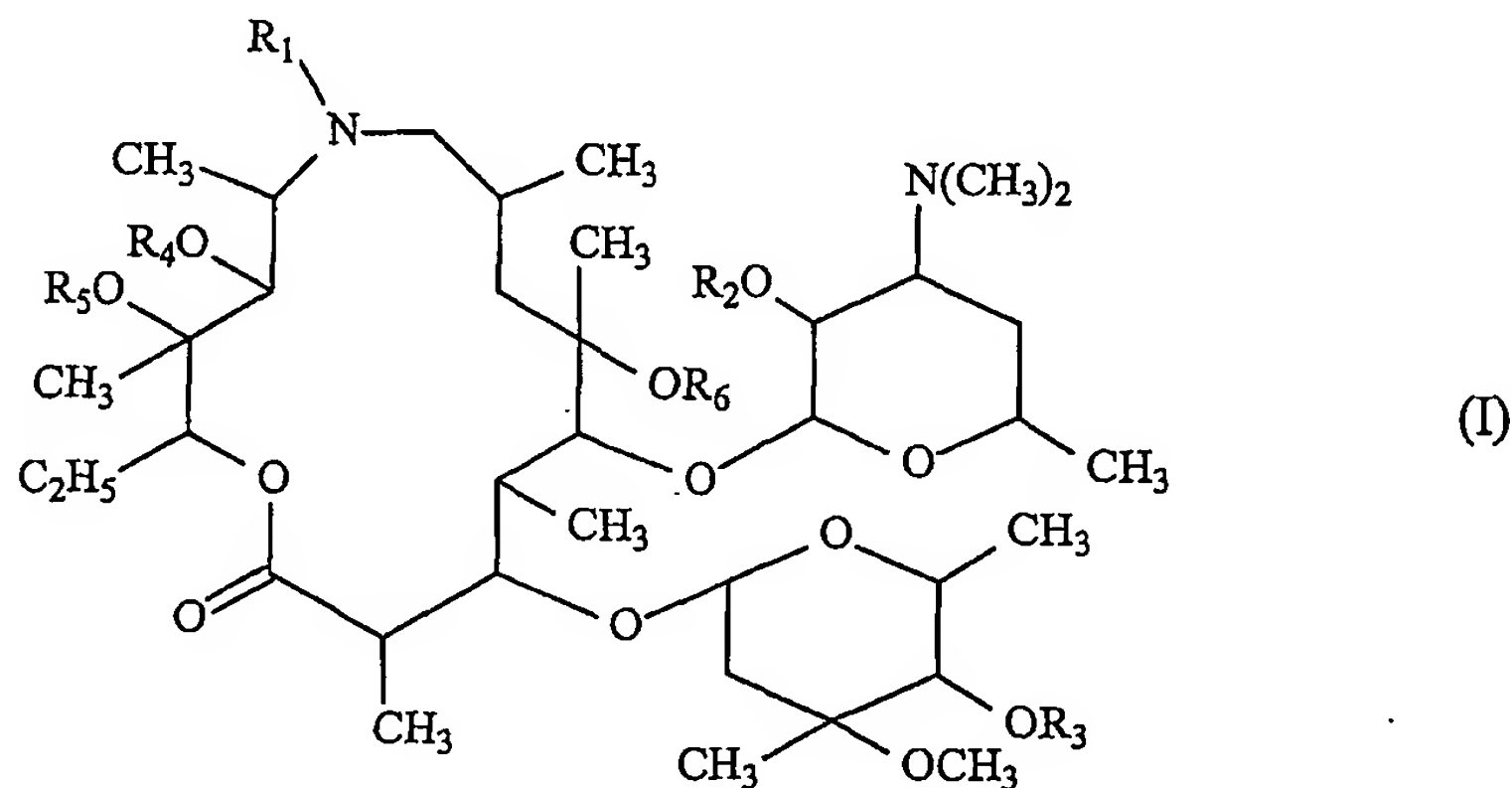
Thus, there is a need for forms of azithromycin that exhibit stability and less variability in the level of hydration.

5

Summary of the Invention

The present invention provides a stable form of azithromycin and analogues thereof. These compounds are in anhydrous form that exhibits increased stability over the corresponding hydrated form. Accordingly, there is provided an anhydrous compound of Formula I:

10



wherein R_1 represents hydrogen, (C_1-C_6) -alkyl, (C_6-C_{10}) -aryl or (C_7-C_{16}) -aralkyl

wherein the R_2 , R_3 , R_4 , R_5 and R_6 groups individually are hydrogen or

15 (C_1-C_6) alkyl. The present invention also provides a process for preparing a compound of Formula I. The anhydrous compound of Formula I is prepared by a process comprising removal of an organic solvent from a solution comprising a hydrated form of the compound of Formula I in the organic solvent or a solution of the hydrated compound of Formula I in a mixture of the organic solvent and

20

water so as to provide the anhydrous compound.

The solvents that are useful in practicing the present invention include any solvent that is capable of co-distilling with water or forming an azeotrope

with water. Non-limiting examples of suitable solvents include alcohols, haloalkanes, esters, ethers or aromatic solvents. Examples of suitable solvents for practicing the invention are C₃-C₆ alcohols such as, for example, n-propanol, 2-propanol, n-butanol, 2-butanol, n-pentanol, 2-pentanol, 3-pentanol and the like; or halo(C₁-C₆)alkanes such as, for example, methylene chloride, chloroform, carbon tetrachloride, 1,1,1-trichloroethylene, 1,1,2-trichloroethylene and the like; esters such as, for example, methyl acetate, ethyl acetate and the like; ethers such as, for example, tetrahydrofuran, tetrahydropyran and the like.

The invention also provides a pharmaceutical composition comprising an anhydrous compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

Additionally, the invention provides a method for treating a microbial infection in a mammal, such as a human, which comprises administering, to a mammal an antimicrobially effective amount of a compound of Formula I in a suitable dosage form.

Brief Description of the Figures

FIG. 1 illustrates the Infrared spectrum of the anhydrous azithromycin of the invention.

FIG. 2 illustrates the Infrared spectrum of azithromycin dihydrate.

FIG. 3 illustrates the DSC spectrum of the anhydrous azithromycin of the invention.

FIG. 4 illustrates the DSC spectrum of azithromycin dihydrate.

FIG. 5 illustrates the XRD spectrum of the anhydrous azithromycin of the invention.

FIG. 6 illustrates the XRD spectrum of azithromycin dihydrate.

Detailed Description

The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo, or iodo. Alkyl denotes both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically

referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active
5 and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by
10 resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine nicotine agonist activity using the standard tests described herein, or using other similar tests which are well known in the art.

15 Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, (C₁-C₆)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, n-pentyl, 2-pentyl, 3-pentyl, or hexyl; halo(C₁-C₆)alkyl can
20 be iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl; C₃-C₆ alcohols can be 1-hydroxypropane, 2-hydroxypropane, 3-hydroxypropane, 1-hydroxybutane, 2-hydroxybutane, 1-hydroxypentane, 2-hydroxypentane, 1-hydroxyhexyl, or 6-hydroxyhexane and the like; aryl can be phenyl, indenyl, or
25 naphthyl.

A specific value for R₁ is CH₃.

A specific value for each of R₂, R₃, R₄, R₅ and R₆ is hydrogen.

A preferred group of compounds are compounds of formula I; or a pharmaceutically acceptable salt thereof.

Another preferred group of compounds are compounds of formula I wherein R_1 is a lower alkyl group having from 1 to 4 carbon atoms and each of R_2 , R_3 , R_4 , R_5 and R_6 is hydrogen.

A preferred compound of the invention is a compound of where R_1 is methyl and each of R_2 , R_3 , R_4 , R_5 and R_6 is hydrogen or a pharmaceutically acceptable salt thereof.

The solvents that are useful in practicing the present invention include solvents that remove water from a solution either by co-distillation or azeotropic distillation. These solvents will remove small amounts of water that are difficult to remove using standard recrystallization techniques.

The preferred alcohol solvents for practicing the present invention are n-propanol, 2-propanol, n-butanol or 2-butanol. Most preferred is 2-propanol.

The preferred haloalkane solvents for practicing the present invention are methylene chloride, chloroform, and carbon tetrachloride. Most preferred is chloroform.

The preferred ester solvents for practicing the present invention are esters such as, for example, methyl acetate, ethyl acetate and the like. The preferred ester is ethyl acetate.

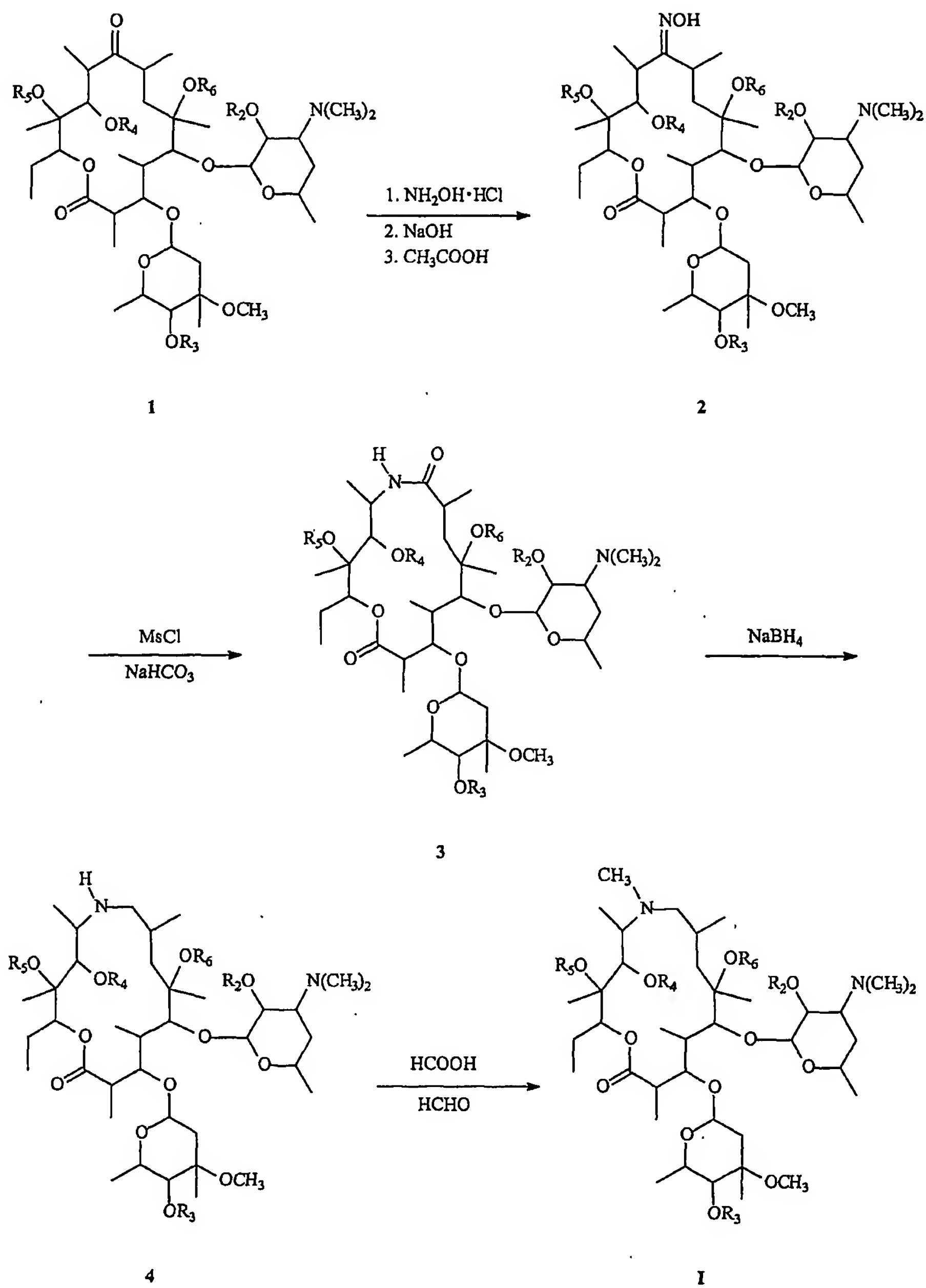
The preferred ether solvents for practicing the present invention are ethers such as, for example, tetrahydrofuran, tetrahydropyran and the like. The preferred ether is tetrahydrofuran.

The preferred aromatic solvents for practicing the present invention are aromatic compounds such as benzene, toluene, xylene and the like. The preferred aromatic solvent is toluene.

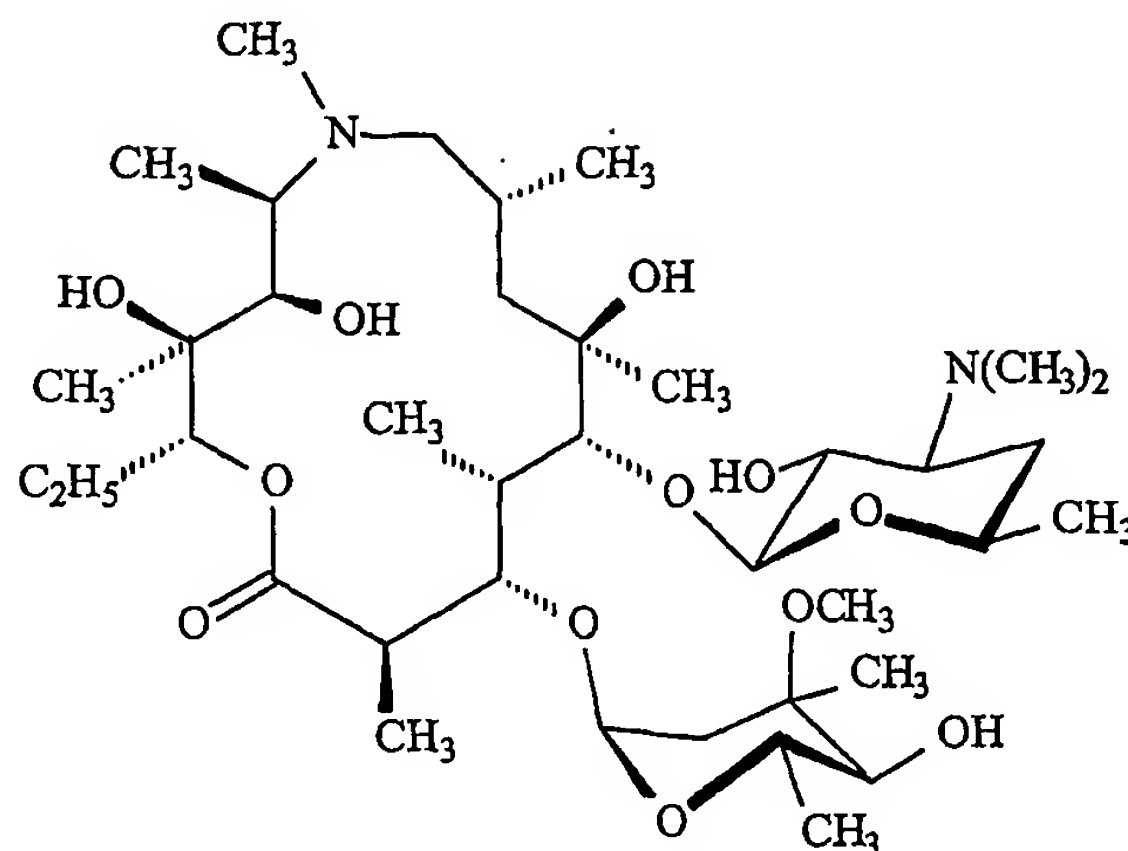
The hydrated compounds useful in practicing the invention can be prepared according to the procedures disclosed in U.S. Patent Nos. 4,328,334, 4,474,768 and 4,517,359. The process for preparing compounds of Formula I is illustrated in Scheme 1. Compound 1, wherein R_2 - R_6 are as defined above is converted to the corresponding oxime, 2 using an excess, *e.g.*, about 10 equivalents, of hydroxyl amine. The oxime is rearranged via the Beckmann rearrangement with methane sulfonyl chloride at low temperature to furnish

amide, 3. The amide, 3 is then reduced, with hydrogen and a catalyst or with a metal hydride, such as sodium borohydride to furnish amine, 4. The amine is then alkylated, *e.g.*, using formaldehyde in the presence of formic acid to form the methyl analogue or by alkylation methods known in the art to form other
5 analogues. The product is crystallized from alcohol/water to provide the hydrated compound of Formula I.

SCHEME 1



A preferred compound of the present invention, Azithromycin, is represented below:



The anhydrous compounds of Formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, *i.e.*, orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, *e.g.*, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit

dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example,

water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the
5 discretion of the attendant physician or clinician.

In general, however, a suitable oral or parenteral dose will be in the range of from about 1 to about 200 mg per kilogram body weight of the recipient per day, preferably in the range of 5 to 100 mg/kg/day, most preferably in the range of 5 to 50 mg/kg/day.

10 The compound is conveniently administered in unit dosage form; for example, containing 25 to 3000 mg, conveniently 100 to 2000 mg, most conveniently, 250 to 600 mg of active ingredient per unit dosage form.

The invention will now be illustrated by the following non-limiting Examples.

15 Example 1.

Erythromycin-A Oxime.

A solution of 1.40 Kg of hydroxylamine hydrochloride in isopropyl alcohol and water was prepared. Sodium hydroxide, 0.81 Kg, was added in portions, at temperature of about 20°C. After the addition, the pH was adjusted
20 to 7.0 with acetic acid. Erythromycin base, 1.5 Kg, was added, and the solution maintained at 45-55°C for 28 hours.

The reaction mixture was cooled to room temperature and the reaction terminated by the addition of ammonia-water mixture. The crude product was treated with water to remove inorganic salts and furnish the title product as a
25 white crystalline material, 1.40 Kg.

Example 2

9a-Aza-9a-homoerythromycin-A.

The title product, prepared in Example 1, 1.25 Kg, was dissolved in acetone and water and maintained at a temperature of 0-5°C. The pH of the
30 reaction mixture was adjusted to about 2.5 to about 2.8 with hydrochloric acid. Sodium bicarbonate, 0.48 Kg, was added in portions to the cooled reaction

mixture. After addition of the sodium bicarbonate, methane sulfonyl chloride, 0.5 Kg, was added. The reaction mixture was stirred for 1 hour at a temperature of 0-5°C. the pH of the reaction mixture was adjusted with aqueous sodium hydroxide and the title product was filtered off as a white crystalline material in high purity. Yield 1.00 Kg.

Example 3

9-Deoxo-9a-aza-9a-homoerythromycin-A.

The title product, prepared in Example 2, 1.00 Kg, was stirred in methanol and water. Sodium borohydride, 1 Kg, was added over four hours. The temperature was maintained below 5°C. After completion of the sodium borohydride addition, the reaction mixture was stirred for an additional six hours at < 5 °C and for an additional twenty-four hours, at room temperature. The reaction was terminated by the addition of water and chloroform. The chloroform layer was separated and fresh water was added. The product was extracted with chloroform by pH adjustment using dilute hydrochloric acid and sodium hydroxide.

Initially, the mixture (water and chloroform) was stirred at pH 2.5 to 2.8 for 1 hour. The pH of the water layer was adjusted to 9.5 to 9.8, and the mixture was stirred for one-half hour. This sequence was repeated with additional chloroform three times. The water layer was separated and an additional portion of chloroform was added and the extraction repeated one additional time. After the extraction, the chloroform extracts were combined, dried over potassium carbonate, filtered and used in the next step without additional treatment.

Example 4

9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin-A.

The title product, prepared in Example 3, was treated with formaldehyde, 0.17 L, and formic acid, 0.105 L, the reaction mixture was stirred for four hours, under nitrogen and heated at reflux for twelve hours. The reaction was cooled, treated with water and the pH was adjusted to 4.0 to 4.5. Chloroform was added and the mixture stirred and the chloroform layer separated. The aqueous layer was adjusted to pH 6.0 to 6.5 and extracted twice with chloroform. Additional

chloroform was added to the aqueous layer and the pH was adjusted with stirring to about pH 2.0 to 3.0 with dilute hydrochloric acid. The mixture was stirred vigorously and the chloroform layer was separated. The pH was adjusted to about pH 6.0 -6.5 with dilute sodium hydroxide and extracted twice with
5 chloroform.

This sequence above was repeated five times on the aqueous layer. The chloroform layers were combined, dried over K_2CO_3 and concentrated under vacuum. The solid residue was dissolved in isopropyl alcohol and the title product crystallized by adding water. The yield of azithromycin was 0.55 Kg.

10 Example 5

Azithromycin Dihydrate.

The title product, 0.5 Kg, prepared in Example 4, was dissolved in water, making the solution acidic (pH of 2.5 to 5.0) with dilute hydrochloric acid. After 20 minutes stirring the pH was raised with dilute sodium hydroxide and the
15 solution was stirred for twelve hours. The product was crystallized as a white crystalline material in high purity. Yield: 0.48 Kg.

Example 6

Anhydrous Azithromycin.

The azithromycin dihydrate, prepared in Example 5, or the azithromycin
20 monohydrate, prepared in Example 4, about 500 g, was dissolved in isopropanol, 3 L. The solution was heated and the alcohol was distilled to remove the water. After the solvent was removed the residue was dried under vacuum to provide the anhydrous azithromycin. Yield 470 g; Purity \geq 96%.

Example 7

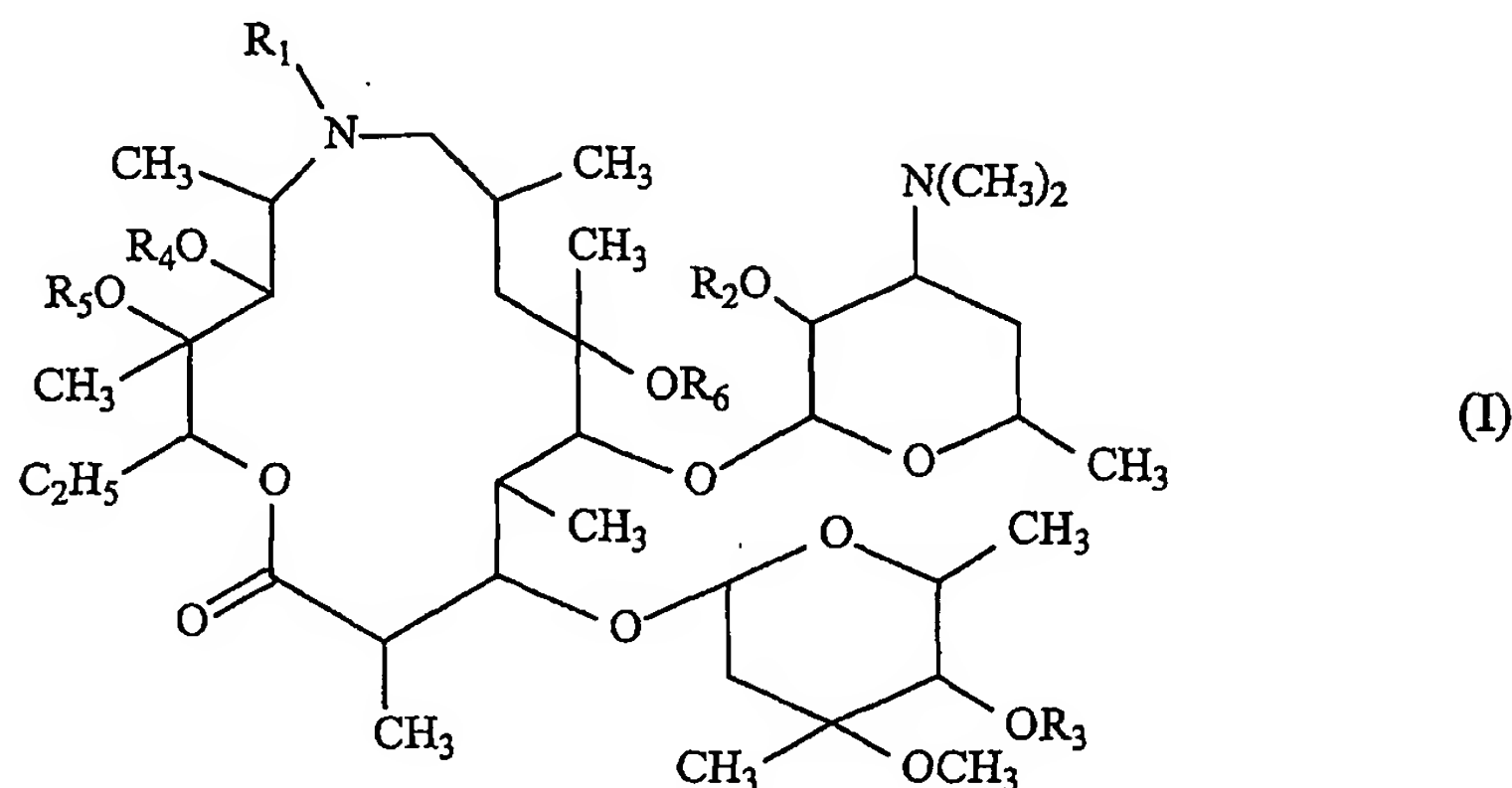
25 **Anhydrous Azithromycin.**

The azithromycin dihydrate, prepared in Example 5, or the azithromycin monohydrate, prepared in Example 4, ~100 g, was dissolved in chloroform and water, 1.7 L (0.7:1). The solution was heated and the solvent was distilled off. After the solvent was removed the residue was dried under vacuum to provide
30 the anhydrous azithromycin. Yield 94 g; Purity \geq 96%.

All publications, patents, and patent documents cited in the specification are incorporated by reference herein, as though individually incorporated by reference. In the case of any inconsistencies, the present disclosure, including any definitions therein will prevail. The invention has been described with
5 reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

Claims:

1. A process for preparing an anhydrous compound having formula I:



wherein R_1 represents hydrogen, (C_1-C_6) -alkyl, (C_6-C_{10}) -aryl or (C_7-C_{16}) -aralkyl:

- 5 wherein R represents an, and each R_2 , R_3 , R_4 , R_5 and R_6 individually represents hydrogen or (C_1-C_4) alkyl; comprising removing an organic solvent or an organic solvent and water from a solution comprising a hydrated compound of Formula I in the organic solvent or the solution of a hydrated compound of Formula I in the mixture of the organic solvent and water so as to provide the anhydrous
- 10 compound.

2. A process according to claim 1, wherein the solution comprises the hydrated compound of Formula I in the organic solvent.

- 15 3. A process according to claim 1, wherein the solution comprises the hydrated compound of Formula I in a mixture of the organic solvent and water.

4. A process according to claim 1, 2 or 3, wherein the solvent is an alcohol, a haloalkane, an ester, an ether or an aromatic compound.

5. A process according to claim 4, wherein the solvent is a C₃-C₆ alcohol, a halo(C₁-C₅)alkane or an aromatic compound.
6. A process according to claim 5, wherein the solvent is selected from the
5 group consisting of n-propanol, 2-propanol, n-butanol, 2-butanol, n-pentanol, 2-pentanol, and 3-pentanol.
7. A process according to claim 6, wherein the solvent is n-propanol, 2-propanol, n-butanol or 2-butanol.
- 10 8. A process according to claim 7, wherein the solvent is 2-propanol.
9. A process according to claim 5, wherein the solvent is a
halo(C₁-C₅)alkane.
- 15 10. A process according to claim 9, wherein the solvent is selected from the group consisting of methylene chloride, chloroform, carbon tetrachloride, 1,1,1-trichloroethylene, and 1,1,2-trichloroethylene.
- 20 11. A process according to claim 10, wherein the solvent is selected from the group consisting of methylene chloride, chloroform, and carbon tetrachloride.
12. A process according to claim 12, wherein the solvent is chloroform.
- 25 13. A process according to claim 5, wherein the solvent is selected from the group consisting of toluene, and xylene.
14. A process according to claim 14, wherein the solvent is toluene.
- 30 15. A process according to claim 1, wherein each R₁, R₂, R₃, R₄, R₅ and R₆ is hydrogen.

16. A process according to claim 1, wherein R_1 is (C_1-C_6) -alkyl, (C_6-C_{10}) -aryl or (C_7-C_{16}) -aralkyl and each R_2 , R_3 , R_4 , R_5 and R_6 is hydrogen.
17. A process according to claim 16, wherein R_1 is (C_1-C_6) -alkyl.
- 5 18. A process according to claim 17, wherein R_1 is methyl or ethyl.
19. A process according to claim 18, wherein R_1 is methyl.
- 10 20. A process according to claim 1, wherein the hydrated compound of Formula I is azithromycin monohydrate, azithromycin dihydrate or a mixture thereof.

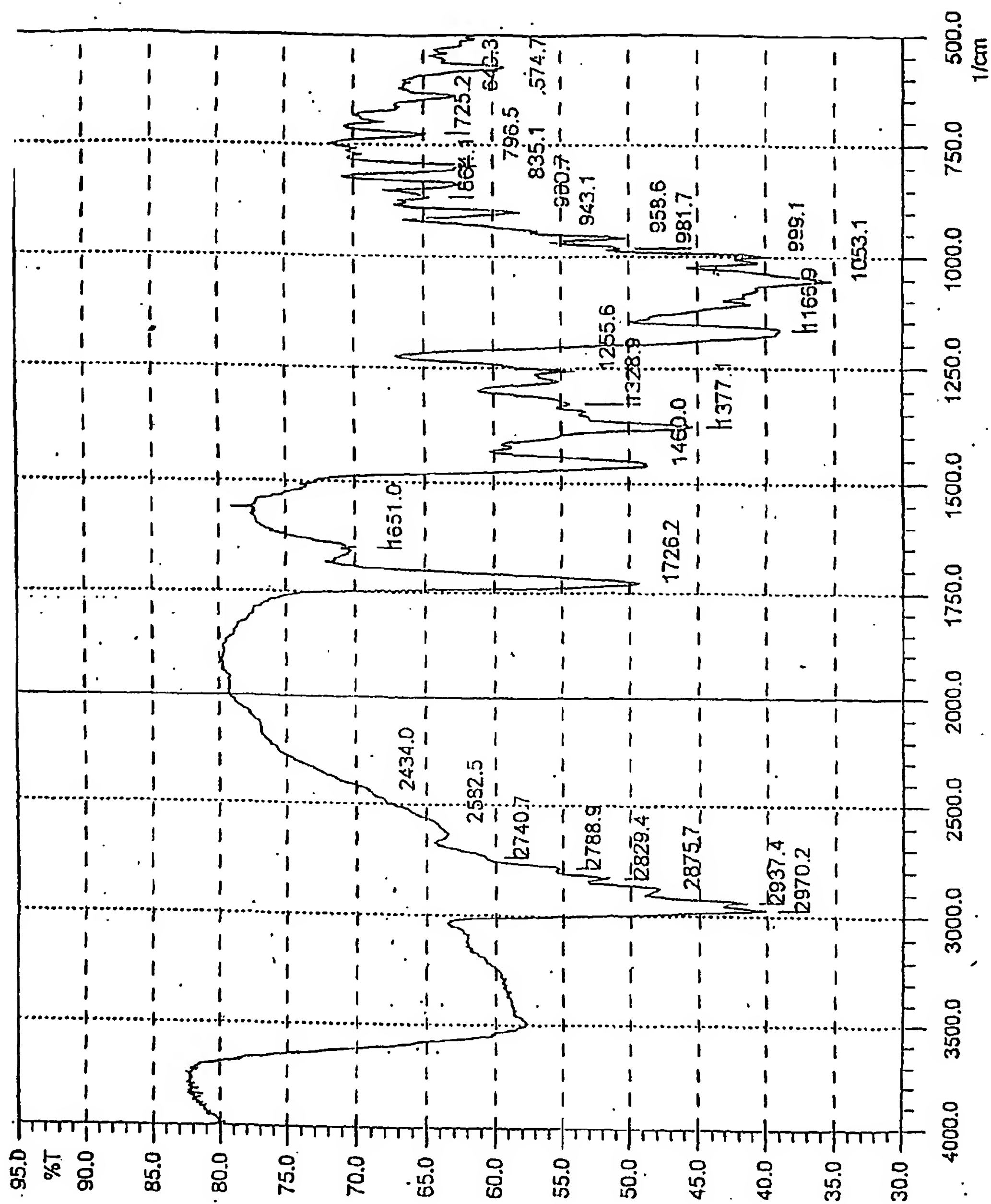


Figure. 1 Infrared spectrum of anhydrous azithromycin.

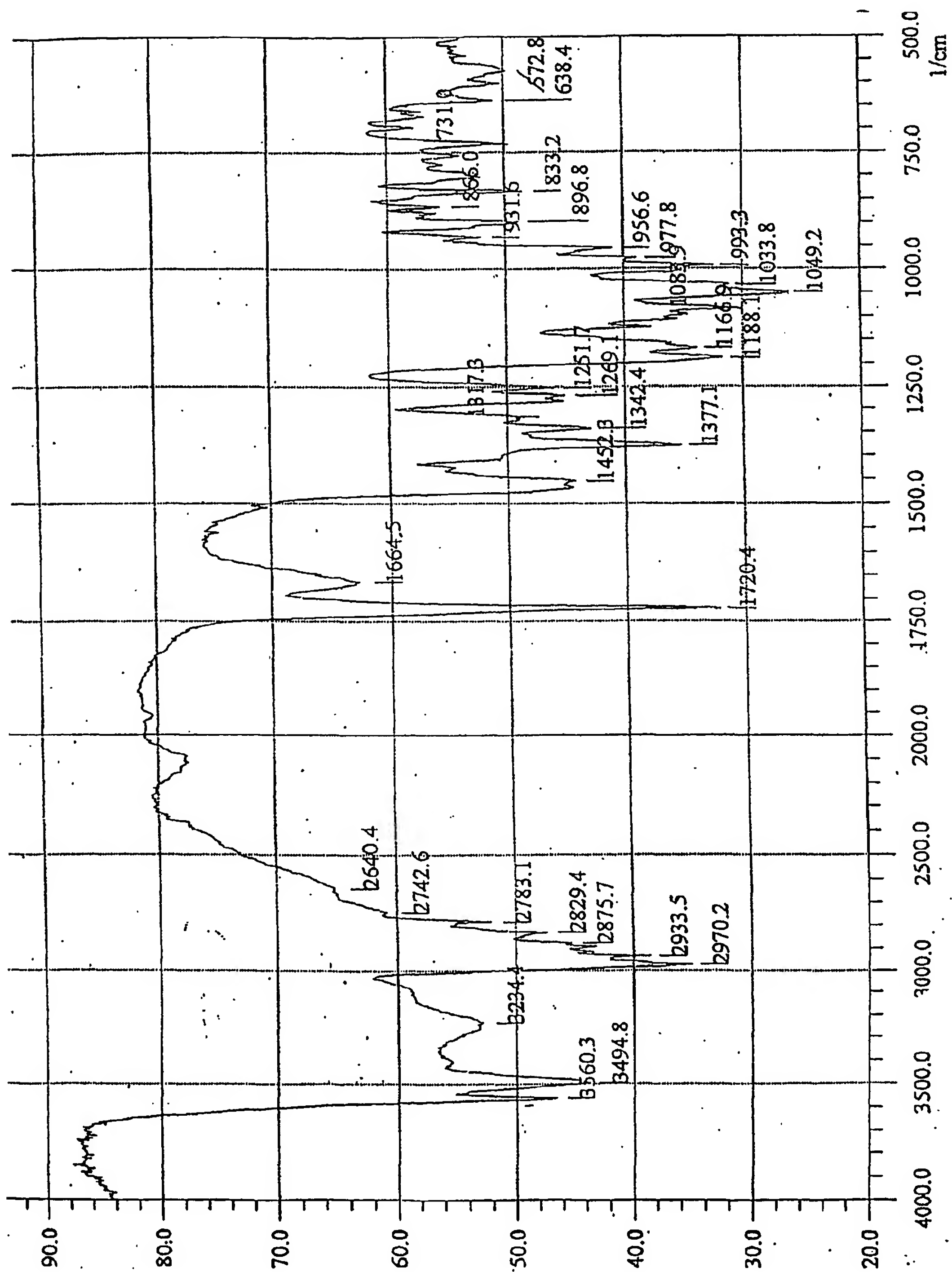
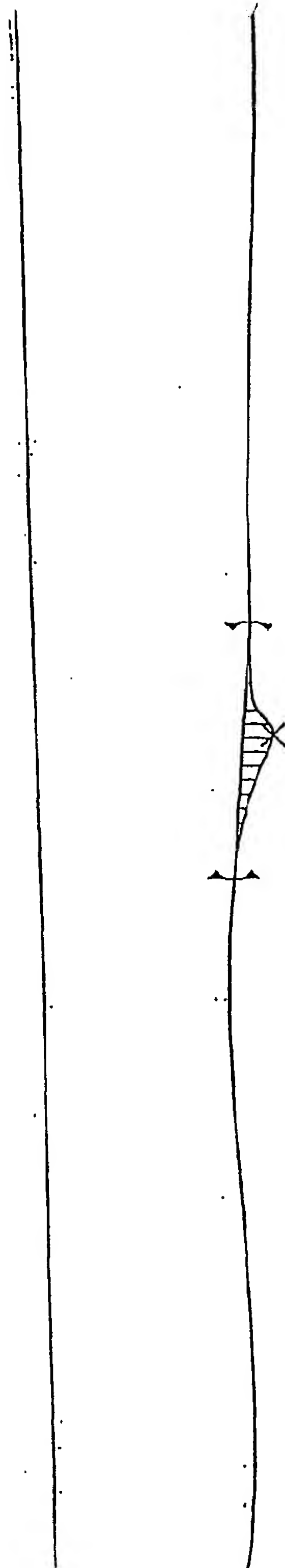


Figure. 2 Infrared spectrum of azithromycin dihydrate.

Figure. 3 DSC spectrum of anhydrous azithromycin.



Integral -9.74 mJ
 normalized -3.75 Jg⁻¹
 Onset 104.24 °C
 Peak 111.79 °C
 Endset 115.34 °C

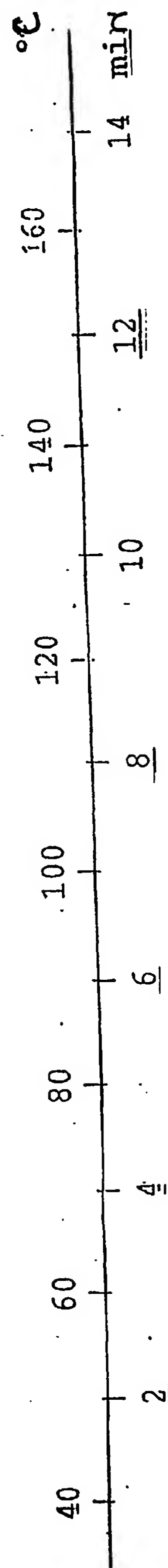
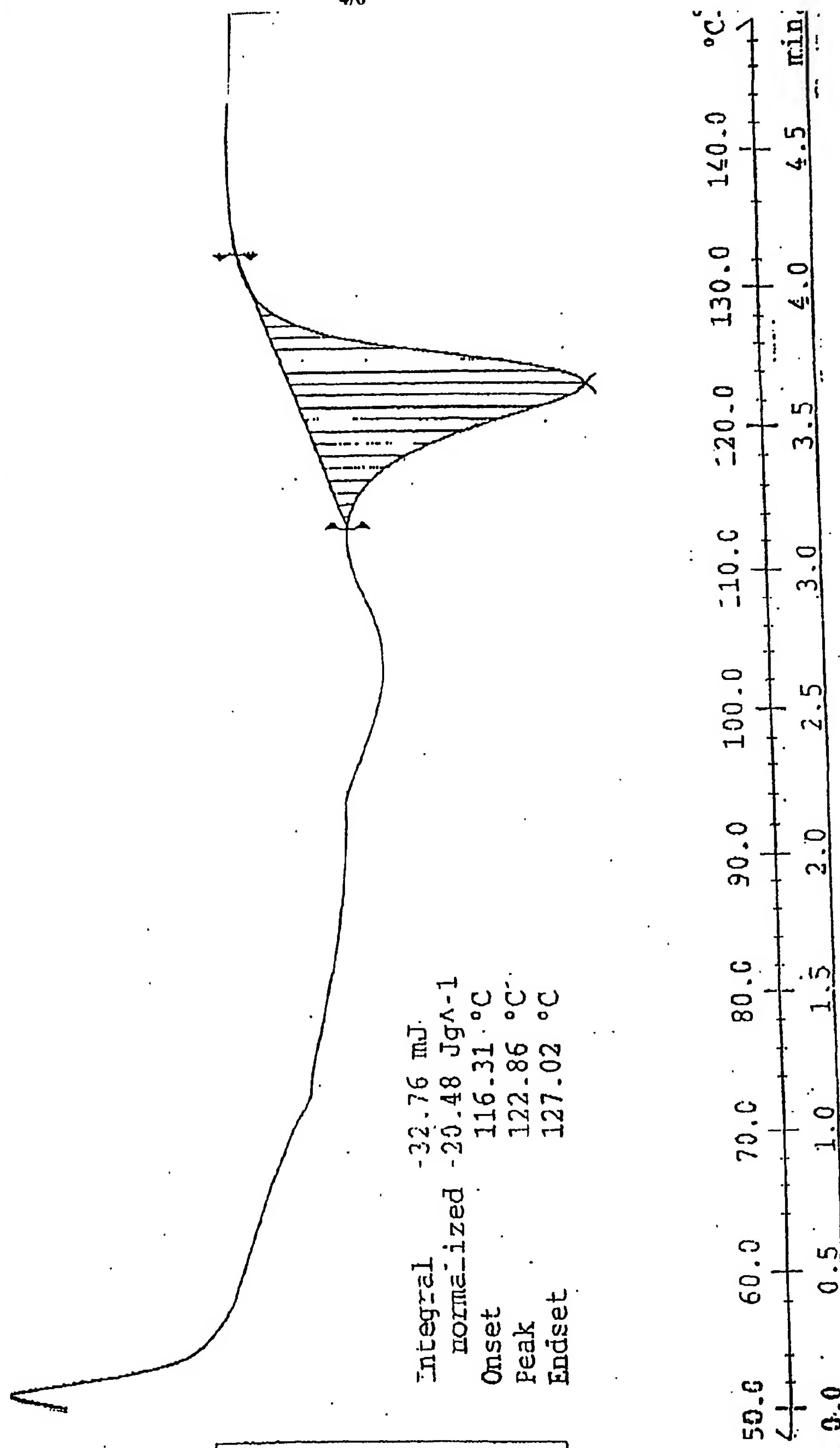


Figure. 4 DSC spectrum of azithromycin dihydrate.



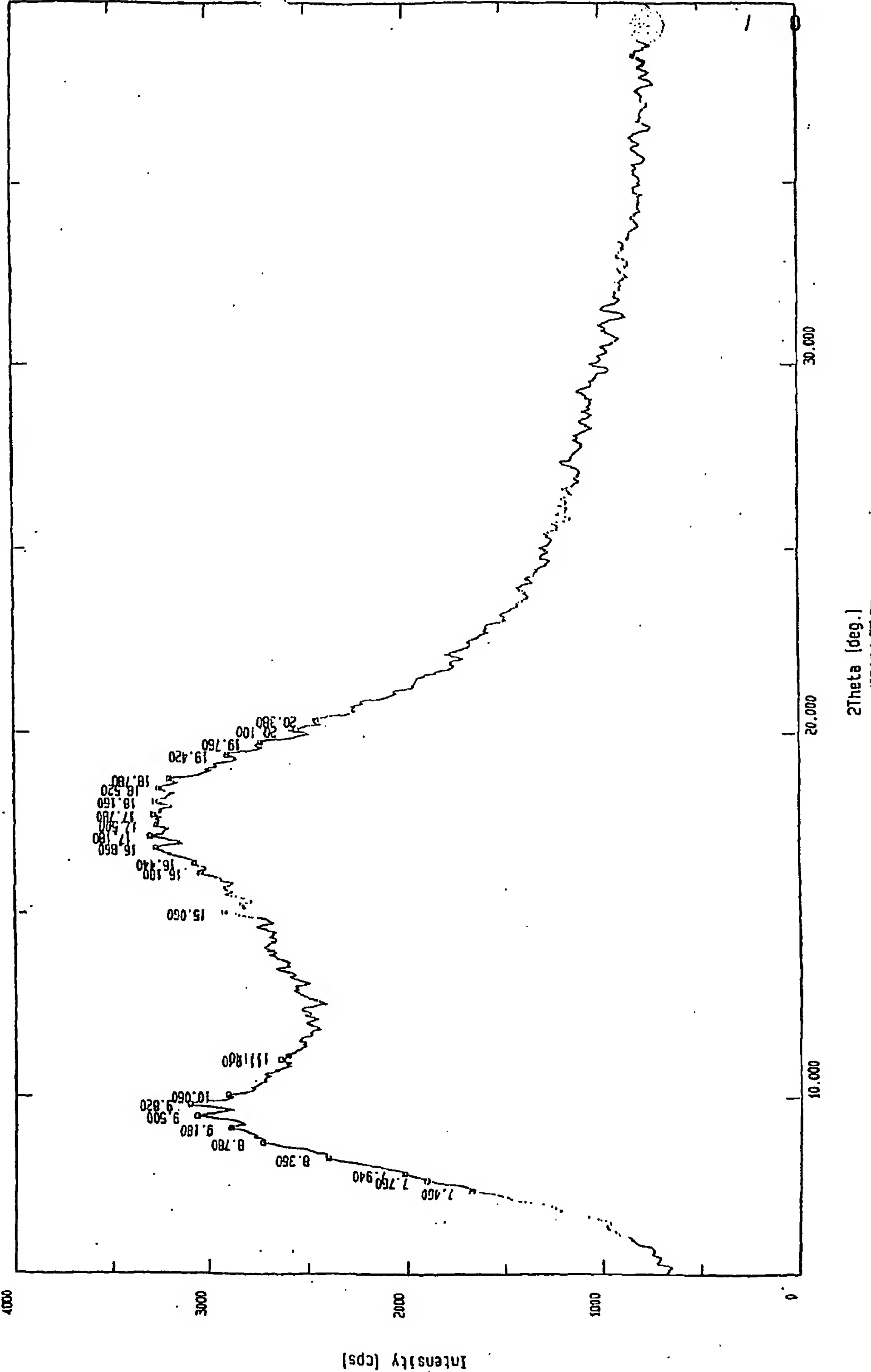


Figure. 5 XRD spectrum of anhydrous azithromycin.

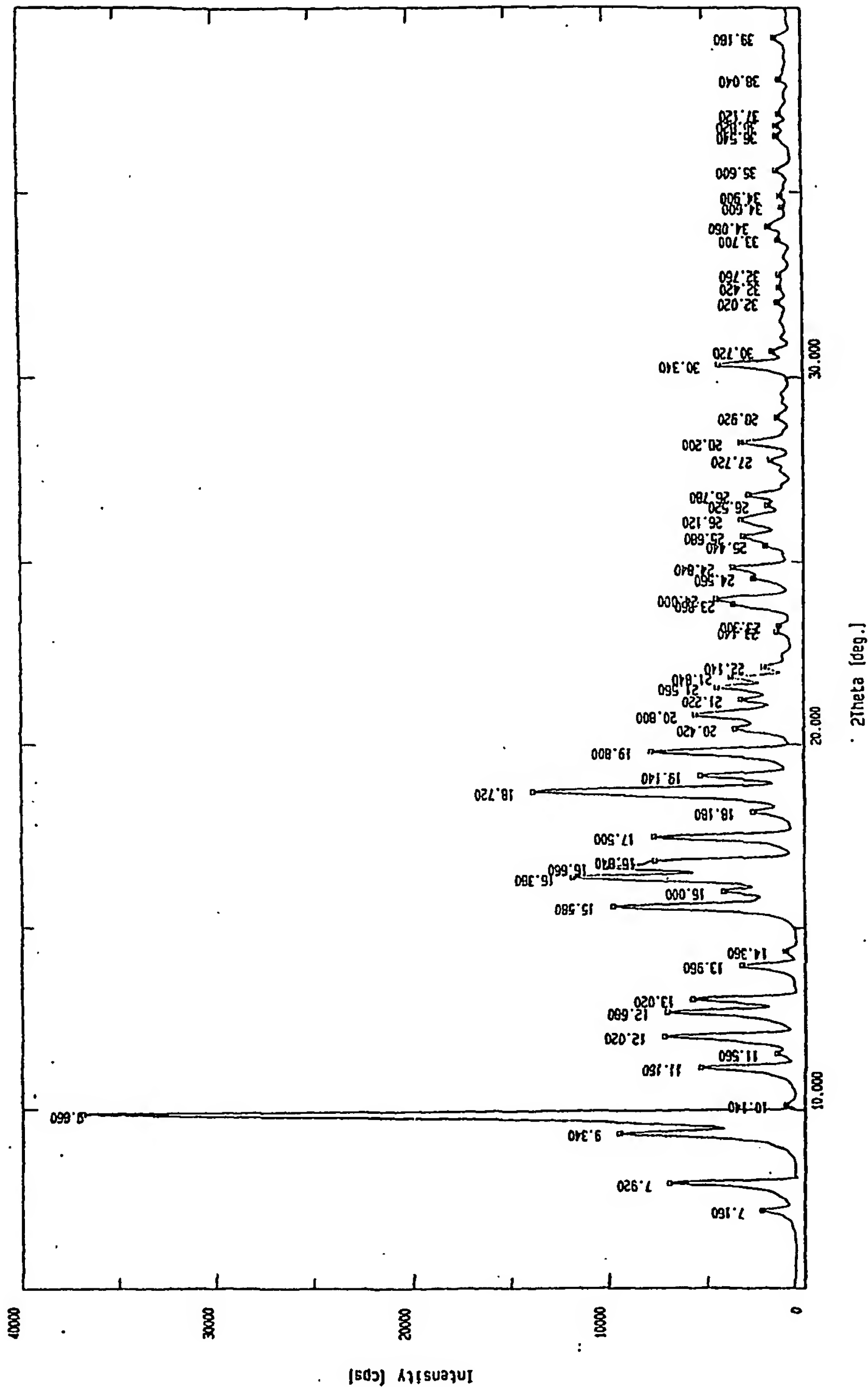


Figure. 6 XRD spectrum of azithromycin dihydrate.

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(54) Title: PROCESS FOR PREPARATION OF ANHYDROUS AZITHROMYCIN

(57) Abstract: The present invention provides a stable form of azithromycin derivatives that act as antibiotics. These compounds are in anhydrous form and have increased stability over the hydrated forms.

INTERNATIONAL SEARCH REPORT

International application No.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 1/00, 17/08

US CL : 536/7.4, 18.5

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 6,245,903 B1 (KARIMIAN et al) 12 June 2001, see column 1, lines 46-58.	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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